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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,879	09/16/2003	Richard R. Tidwell	421/60/10/2	3104

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EXAMINER	
FISHER, ABIGAIL L	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/663,879	TIDWELL ET AL.	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-31 and 49* is/are pending in the application.

4a) Of the above claim(s) *20-28 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-19, 29, 31 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments and Remarks filed on October 15 2008 is acknowledged. Claims 1-16 and 32-48 were/stand cancelled. Claim 49 was added. Claims 17-31 and 49 are pending. Claims 20-28 and 30 are withdrawn as being directed to a non-elected invention. Claims 17-19, 29, 31 and 40 are directed to the elected invention.

Allowable Subject Matter

The indicated allowability of claims 18-19, 29, and 31 are withdrawn in view of newly cited art as well as reconsideration of the instantly claimed invention. Rejections based on the newly cited reference(s) follow.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-19, 29, and 31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The specification by way of the prior art is enabling for the treatment of Alzheimer's disease with pentamidine, butamidine and the other structural analogs of pentamidine found in Fig 1 of Reynolds et al. (Eur. J. Pharmacology, 1993), however, the specification does not reasonably provide enablement for the treatment of

Alzheimer's with any bis-benzamidine or all of the compounds of the genus of instant claim 18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Formal, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

The nature of the invention, relative skill level, and breadth of the claims

The instant invention is directed to a method for treating Alzheimer's disease in a subject in need of treatment comprising administration of a bis-benzamidine compound or a compound of Formula I.

The complex nature of the claims is greatly exacerbated by the breath of the claims. The claims encompass utilizing a large genus of compounds in the treatment of Alzheimer's disease. The relative skill of those in the art is high, that of an MD or PHD.

The state and predictability of the art

Reynolds et al. recognize that certain drugs such as pentamidine can be utilized to treat Alzheimer's disease. The Merck Manual indicates that current treatment regimes for Alzheimer's disease are utilized to slow the progression of the disease. However, no currently available drug has consistently proved to be effective. Furthermore, treatment varies significantly from person to person. One third of people do not benefit from drug treatment and about one third improve slightly for only a couple of months (See Treatment section). Furthermore, as evidenced by Roses et al. (Alzheimer's and Dementia, 2006), it is known that although Alzheimer's disease was described nearly

1000 years ago the disease still remains difficult to treat. It is specifically taught that in this highly unpredictable world of drug discovery and therapy it is unknown whether, when or which one of several therapeutic strategies, targets, or molecules may ever result in an effective drug (page 59, left column, first paragraph). Therefore, the state of the art recognizes that treatment of Alzheimer's disease is difficult

The lack of significant guidance from the specification or the prior art with regard to how to treat Alzheimer's disease utilizing the claimed amidine compounds makes practicing the scope of the invention unpredictable.

The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for how to use the compounds to treat Alzheimer's disease. The working examples clearly show that these compounds bind to the imidazoline receptor. However, the specification generally teaches that in patients with Alzheimer's the expression if I_2 binding is upregulated. However, no guidance is given as to how that correlates with the treatment of Alzheimer's disease. No guidance is given to show that binding of the imidazoline receptor results in compounds that are effective in the treatment of Alzheimer's disease. Furthermore, the examiner can find no art, whether published prior to the filing of this application or after the filing of the application that supports the notion that binding of the imidazoline receptor results in an effective treatment for Alzheimer's disease.

The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used to treat Alzheimer's disease as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-19, 29, 31 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite that the "amidine compound comprises". The claims are directed to a chemical compound, which is one entity. A compound is a particular structure. The claims are indefinite because they recite that the compound "comprises". This renders the claims indefinite because it is unclear what else the compound comprises. Typical language for US practice utilized is that a composition comprises. However, the instant claims recite that a "compound comprises", which is a single entity and therefore can not comprise something else.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claim 17 under 35 U.S.C. 102(b) as being anticipated by Anderskewitz et al. (WO 97/216760) is **withdrawn** in light of Applicant's amendments filed on October 15 2008.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-19, 29, 31 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds et al. (Eur. J. Pharmacology, 1993) in view of Chenard (US Patent No. 5498610)

Applicant Claims

Applicant claims a method for treating Alzheimer's disease comprising the administration of a bis-benzamidine compound or an amidine compound of formula I. Specific amidine compounds claimed include pentamidine.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Reynolds et al. is directed to the study of the effects of pentamidine and several analogs on the NMDA receptor. Pentamidine is a potent and efficacious NMDA receptor antagonist and was found to be neuroprotective in vitro (page 175, right column, first paragraph). The analogs of pentamidine tested are found in Figure 1. Table 1 shows the effects of the respective compound in the inhibition of the NMDA receptor as well as the neuroprotection ability of these specific compounds. All of the compounds were found to be effective in inhibiting the NMDA receptor. It is taught that

the NMDA receptors are involved in the pathology of a number of neurological disorders such as Alzheimer's disease (page 175, left column, first paragraph).

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Reynolds et al. do suggest that the compounds can be utilized to treat Alzheimer's disease, Reynolds et al. do not exemplify utilizing the compounds to treat Alzheimer's disease. However, this deficiency is cured by Chenard.

Chenard is directed to the method of treating diseases or conditions susceptible to the treatment of blockage of the NMDA receptor. These diseases as claimed include Alzheimer's disease (claim 7). Furthermore, it is generally taught that it is known in the art that antagonists of NMDA receptors are useful therapeutic agents for the treatment of neurological disorders. As several patents are directed to the effectiveness of NMDA receptor antagonists in the treatment of neurological disorders such as Alzheimer's disease (column 2, lines 1-14).

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Reynolds et al. and Chenard and utilize pentamidine and its analogs in a method of treating Alzheimer's disease. One of ordinary skill in the art would have been motivated to utilize pentamidine and its analogs in a method of treating Alzheimer's disease as Reynolds et al. teach that the compounds are effective antagonists of the NMDA receptor and suggest that inhibition

of this receptor can be utilized to treat Alzheimer's disease. Furthermore, Chenard teaches that it is known in the art that inhibition of the NMDA receptor can be utilized to treat neurological disorders such as Alzheimer's disease. Therefore, it would have been obvious to one of ordinary skill in the art to utilize these compounds in a method of treating Alzheimer's disease.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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